THE ENERGY COST OF THE EXCRETION OF URINE

BY HENRY BORSOOK AND HOWARD M. WINEGARDEN

KERCKHOFF BIOLOGICAL LABORATORIES, CALIFORNIA INSTITUTE OF TECHNOLOGY

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It has been shown that the work performed by the normal kidney in man in the excretion of urine is of the order of magnitude of 0.7 gram calories per cc. of urine; or 70 gram calories per gram of nitrogen excreted. It is instructive to compare the quantity of work performed by the kidney with the energy consumption of the kidney during the performance of this work.

The energy consumption of the kidney has been estimated by a number of experimenters and by different methods; and the values obtained are all of the same order of magnitude. The concordance of these values justifies an estimate of the efficiency of the kidney, i.e., of the ratio of the work performed, calculated from the constitution of the urine, to the energy used. The efficiency of the kidney, defined in this way, appears, even in health, to be about 1–2 per cent. So far as the authors are aware, there are no data inconsistent with this low figure. Rather the reverse, this association of the thermodynamic work with the observed energy consumption of the kidney permits the correlation of a large number of facts regarding the behavior of the kidney in health and disease.

The earliest measurements of oxygen consumption of the kidney are those of Barcroft and Brodie[15,16], and of Barcroft and Straub.[17] These show that the metabolism of the kidney is increased when it is performing work, i.e., when it is producing a urine in which the dissolved substances are present in greater concentrations than in the plasma. Barcroft and Straub found, for example, that the excretion of large quantities of chloride in the urine, in concentrations nearly the same as that in the plasma, was not accompanied by an increase in the consumption of oxygen; while the excretion of sulfate or of urea in the urine, in much greater concentration than in the plasma, was attended by large increases in the oxygen consumption. These results might have been predicted from thermodynamic theory. The association of increased oxygen consumption only with increased work, is strikingly exhibited in the behavior of the kidney damaged in various ways, as by caffeine, mercuric chloride, bleeding, or dilution of the blood or plasma with saline. Under these conditions the oxygen consumption of the kidney was not increased when diuresis was induced by sulfate or urea, and at the same time these substances were not concentrated in the urine as they were by the undamaged kidney, but were passed in nearly the same concentrations as in the plasma. In one case a larger quantity of sulfate was excreted at a low concentration,

without increased oxygen consumption, than in another where there was a large increase in the oxygen consumption, and a high concentration of the sulfate in the urine. The observations of Barcroft and Straub have been confirmed by Knowlton and Silverman[18] and by Bainbridge and Evans[19] (in one case on the isolated kidney). Winfield[20] found that the oxygen consumption of the kidney fell to $^1/_4$–$^1/_5$ of its normal value when the urine became isotonic after the intravenous injection of saline.

The dependence of the concentrating function of the kidney on concomitant oxidations is strikingly illustrated in the effects of cyanide on the kidney. Starling and Verney[21] observed, after the addition of KCN to the circulating blood in a heart-lung-kidney preparation, that the NaCl concentration in the urine rose to that in the plasma, i.e., the "concentration" of water fell to that of the serum, while the concentrations of urea and of sulfate fell markedly. On changing the circulating blood to one free from KCN, the chloride concentration fell again to a value not far from the original level, while the urea and sulfate concentrations rose a little, the sulfate more than the urea, toward their former levels. Similarly the power of the kidney to excrete and concentrate phenol red was also markedly reduced after poisoning with cyanide. The observations of Marshall and Crane[22] are essentially the same. These observers found that the urine contained approximately the same amount of water chloride, and bicarbonate after a period of temporary asphyxia induced by occlusion of the renal artery for 20 minutes, but much less urea, phosphate sulfate, creatinine and ammonia.

Three groups of workers claim to have been unable to confirm the observations described above. The first apparently contradictory results were those obtained by Tamura and Miwa.[23] It is not possible to interpret their results, or to compare them with those of Barcroft and Straub, first, because the urine analyses are not given. For example, if the excretion of urea is markedly reduced during a sulfate diuresis, it is possible that in spite of an increased excretion of sulfate, the total work performed by the kidney may be reduced; or a great change in the urinary chloride concentration may change the sign of the free energy term for the excretion of water. Tamura and Miwa found, in the rabbit, that diuresis induced by sulfate and caffeine, did not increase the oxygen consumption, while diuretin and salicylates provoked large increases. The employment of different animals by the two groups of experimenters, the rabbit in the experiments of Tamura and Miwa, the cat and dog in the experiments quoted here performed by Barcroft and Brodie, and Barcroft and Straub, is the second condition which prevents a comparison of the results obtained. The following typical observations show the distinct differences in function between the rabbit kidney on one hand, and the kidney of carnivora or omnivora on the other. After the injection of massive doses, the data of

Mayrs[45] show in the rabbit urea concentrated in the urine to only three times its concentration in the plasma, sulfate six times, phosphate four to five times and creatinine four times. On the other hand, in the urine of the dog, cat or man, urea may be concentrated sixty times, sulfate one hundred times, phosphate twenty times, and creatinine one to two hundred times the concentration in the blood. The experiments of Frandsen[24] show that the excretion of ingested sodium chloride or urea is very slow in the normal rabbit. Frandsen found in two experiments an average increased hourly excretion of only 0.016 and 0.017 gm. of nitrogen, respectively, in the four-hour period after the ingestion of 0.75 gm. of urea in addition to the usual ration. In another experiment in which a rabbit received 1.0 gm. of urea 3 hours after the routine meal, there was a uniform increased excretion of 0.052 gm. of nitrogen during the next four hours. It is possible, therefore, that in spite of the diuresis observed, the amount of the injected substances actually excreted in the experiments of Tamura and Miwa was not greatly increased. In view of the relatively slight degree to which substances are concentrated in the urine of the rabbit it seems probable, further, that the formation of urine by the rabbit's kidney entails considerably less work than is the case in carnivora or omnivora; and accordingly, the experimental error in the detection of differences is magnified.

Recently Hayman and Schmidt[25] described experiments in which "the injection of urea, caffeine, sodium sulfate, or certain drugs was not followed by any characteristic effect on apparent oxygen metabolism." Their protocols show that in four experiments out of six, caffeine was administered 10–20 minutes before sodium sulfate; here sodium sulfate did not elicit any increased consumption of oxygen, even though the flow of urine was increased. In one of the remaining experiments, in which the injection of sulfate was not preceded by caffeine, the protocol gives the largest value for oxygen consumption recorded in their experiments. The observations of Hayman and Schmidt, therefore, as described in their protocols, confirm the observations of Barcroft and Straub, "that caffeine virtually abolished the specific effect of sodium sulfate," of increasing the oxygen consumption of the kidney. Furthermore the experimental procedure of Hayman and Schmidt was rather drastic. In one experiment within a period of two hours after the completion of the operation, there were injected 150 cc. blood, 165 cc. saline, 80 mgm. caffeine, 20 cc. of 20 per cent sodium sulfate, pituitrin, adrenalin, and morphine. For this reason it is difficult to interpret the observations of Hayman and Schmidt. Hardly enough time, it seems, was allowed for the effect of one of the injected substances to manifest itself, before another was injected; much longer time was allowed in the experiments of Barcroft and Straub. In addition the data of the urine analyses are not given.

Fee[26] (1929), using a heart-lung-kidney preparation, obtained results which were taken to confirm the negative results reported by Hayman and Schmidt. Fee's statement is that "the actual excretion of large amounts of sulfate by the kidney is not attended with an increase in the renal oxygen consumption unless there is a concomitant increase in renal blood flow." It is questionable if the results of experiments on a heart-lung-kidney preparation may be compared with those obtained by Barcroft and Straub with the kidney *in situ*. Starling and Verney, and Fee and Hemingway[27] found that the urine from the heart-lung-kidney preparation is hypotonic, while the healthy mammalian kidney *in situ*, of course, excretes hypertonic urine. The production of either hypertonic or hypotonic urine is attended with an increased oxygen consumption; when the hypotonicity is reduced in the isolated kidney, by pituitrin for example, the oxygen consumption is also decreased. It is possible that the injection of sulfate under these conditions has the same effect as pituitrin, i.e., increases the concentration of salt in the hypotonic urine, rendering it more nearly isotonic, and thereby reduces the work and the oxygen consumption of the kidney. It is difficult to obtain a clear interpretation of the results reported by Fee, because the analyses of the urine, in detail are not given. The analysis of the work of secretion of hypotonic urine, below, shows that under the conditions of this experiment the result to be expected of an increased concentration of sulfate, from thermodynamic considerations, may be a reduced rather than an increased consumption of oxygen, due to a large decrease in the work of excretion of water. The results as given, therefore, may be taken to confirm, rather than to disagree with the hypothesis that increased work by the kidney is attended by a demonstrably increased consumption of oxygen. It is not certain, moreover, that the kidney in these experiments was in a "normal" state; the experiment reported in detail "was terminated by oedema" within less than an hour after the injection of the sulfate. More weight may therefore be placed on the observations on the effects of cyanide by Starling and Verney on the same kidney preparation as used by Fee.

Further confirmation of this hypothesis, that work of concentration entails increased metabolism in the kidney, is contained in the observation by Barcroft and Brodie of a large increase in renal oxygen consumption during phlorhizin glycosuria. In phlorhizin glycosuria the concentration of sugar in the urine may become very high, one hundred times that in the plasma; while the total nitrogen, urea, phosphates, and chlorides show no significant change. The observation of an increased oxygen consumption when sugar is excreted in highly concentrated solution is significant here, because the severely damaged kidney excretes approximately an isotonic urine, containing sugar in the same concentration as in the plasma; and its oxygen consumption is markedly reduced.[21]

The production of hypotonic urine, can be shown by the same method as that employed in the previous communication to entail work on the part of the kidney; and may, therefore, be expected to be attended by an increased consumption of oxygen. Only the excretion of a strictly isotonic urine, intermediate between the extremes of hyper- and hypotonicity, entails no work by the kidney. This can be illustrated by assuming an extreme case, a "urine" consisting only of a 1 per cent solution of urea; in which the mol fraction of water, therefore, is approximately 0.997. The free energy change for the transport of the water in a liter of such "urine" is now negative instead of positive, amounting to about −100 calories; $-\Delta F$ for urea is −430 calories. The total of −530 calories is of the same order of magnitude as the total free energy for the production of one liter of average hypertonic urine. This is due to the fact that a relatively large quantity of water is transported from a lower concentration in the plasma to a higher concentration in the urine. Further, the conditions under which such a urine is produced are usually those of diuresis so that the value of N for water especially is greatly increased, with the result that the work of the kidney per unit time is quite large. The tonicity of the urine depends mainly upon the sodium chloride and the urea; when the urea excretion is constant and its concentration in the urine is less than the total molecular concentration of the plasma, the concentration of sodium chloride as a rule determines whether or not work is done in the transport of water from the plasma to the urine. When the chloride concentration is low, so that the mol fraction of water in the urine is greater than in the plasma, the kidney performs work in transporting water from plasma to urine. On the other hand, when the concentration of chloride in the urine is greater than in the plasma, so that the mol fraction of water is less in the urine than in the plasma, water is "diluted" in passing from plasma to urine, and $-\Delta F$ becomes positive for the transport of water, i.e., the kidney "gains" work.

The physiological evidence bearing upon this aspect of renal function, the work of secretion of hypotonic urine, is not abundant; but as far as it goes it is completely confirmatory of the above thermodynamic predictions. The urine of the frog is always hypotonic to the plasma; and the concentration of nitrogen is practically the same as the non-protein nitrogen in the blood.[28] When the frog's kidney is poisoned with caffeine, or corrosive sublimate, the concentration of salts in the urine approximates that in Ringer's solution. After the administration of cyanide "the fluid issuing from the ureter comes to resemble the glomerular filtrate, sugar tends to appear in the urine, the chloride is less reduced than usual, potassium and calcium tend to approach the concentration of the perfusing fluid, and urea is no longer concentrated."[1] Narcotics, which Keilin[29]

recently has shown are selective poisons for one type of widely distributed oxidation mechanism, have the same effect as cyanide.

The isolated mammalian kidney, perfused by the heart-lung preparation as mentioned above, resembles a frog's kidney in that the urine secreted is hypotonic with respect to salts, although urea and sulfate are concentrated to a considerable extent. Starling and Verney found that this kidney after being poisoned with cyanide passed a urine which was isotonic with respect to the serum in every detail. Similarly, Fee and Hemingway working with the same heart-lung-kidney preparation found that the oxygen consumption increased as the urine contained less and less chloride. The significance of this observation is augmented by the fact that the oxygen consumption of the damaged or diseased kidney is less than normal.[17,39,40] When pitruitrin was added to the perfusing fluid in the experiments of Fee and Hemingway[27] the chloride concentration rose, and at the same time the oxygen consumption became less.

The evidence, therefore, seems clear that the performance of what may be called thermodynamic work by the kidney involves an expenditure of energy which is derived from oxidations within the renal cells. It is instructive, therefore, to compare the work performed by the kidney with the energy used, i.e., to determine the "efficiency" of the kidney.

The discussion of the relationship between the work performed and the energy used by the kidney is facilitated by the following explicit definition of the terms employed and the assumptions made.*

W = Minimum work necessary to produce 1000 cc. *urine* from infinite quantity of *blood* of character entering kidney.

W_1 = Minimum work necessary to produce 1000 cc. *urine* + venous blood from the actual quantity of *blood*.

$W_1 \approx W$. The justification for this assumption has been discussed in the previous communication.

Q = Heat of combustion of fuel burned while 1000 cc. urine are excreted.

Q_1 = Maximum work available from this combustion. In a previous communication[46] it was shown that the free energy of combustion of fat and of glucose in the body was, in each case, nearly equal to the heat of combustion. No data are available regarding the free energy of combustion of the proteins. But is probable that no error is involved in assuming that $Q_1 \approx Q$.

Q_m = Heat of combustion of fuel used in maintaining the kidney alive for the length of time necessary to produce 1000 cc. of urine but not connected with the production of urine.

Q_{iso} = Additional heat of combustion required to produce 1000 cc. urine of such character that $W_1 \approx W = 0$. For practical

purposes this may be taken to represent the additional heat produced by the kidney in the formation of 1000 cc. isotonic urine.

The efficiency, E, is a conventional term, which may be defined in a number of ways. Three possibilities are: $E = \frac{W}{Q}$; $E' = \frac{\Delta W}{\Delta Q}$, where Δ is the change accompanying any change in the blood and urine; and $E'' = \frac{W}{Q - (Q_m + Q_{iso})}$. It is obvious that only E' may be expected to show any degree of constancy with variation in the amount of work performed, i.e., with large variations of ΔW.

The values for the rate of metabolism of the kidney determined by a number of different methods are remarkably concordant: Barcroft and Brodie, and Barcroft and Straub observed rates of oxygen consumption per gram of "resting" kidney per minute, ranging from 0.008 to 0.075 cc. in the dog, from 0.03 to 0.12 cc. in the cat, and from 0.046 to 0.13 cc. in the rabbit. Fee and Hemingway obtained similar values for the isolated kidney (presumably of the dog) of 0.03 to 0.2 cc. per gram per minute. The term "resting" value, is to some extent a misnomer here, because the kidney even at rest is producing urine; and it is possible that the bulk of the urine excreted in a day is elaborated by the "resting" kidney i.e., not in a state of diuresis. For the purpose of estimating the order of magnitude of renal efficiency in man, we have taken as an average value for the rate of oxygen consumption of the kidney over 24 hours the relatively low figure of 0.03 cc. per gram per minute; and an average weight for the human kidney of 150 grams.[30] On this basis the renal oxygen consumption in man in 24 hours is of the order of magnitude of 13 liters. Assuming an R. Q. of 0.80, the caloric equivalent of this quantity of oxygen is 62 kg. calories.[31] Since the total work performed by the kidney as set out in table 2 of the previous communication is 704 gram calories, the "efficiency" of the kidney, i.e., W/Q, is approximately 1 per cent. Barcroft and Brodie calculated from their experiments ratios of work performed to energy consumed during periods of diuresis, i.e., $\Delta W/\Delta Q$, and obtained values for urea excretion of 1.75 and 0.14 per cent; it should be mentioned that, because these values for renal efficiency are so low, Barcroft and Brodie hesitated to accept them as correct. Nevertheless, as pointed out before, the total of 704 gram calories represents probably all but a negligible quantity of the work performed by the kidney, and the values employed for oxygen consumption are low rather than high. During diuresis Barcroft and Brodie found that the oxygen consumption of the kidney may be relatively 5–10 times greater than the oxygen consumption of the body as a whole.

Janssen and Rein[32] recently attempted to determine the metabolism of the kidney by measuring the difference in temperature between the

arterial and venous blood. They obtained values for the metabolism of the kidney of a similar order of magnitude as those above.

In view of these low calculated values of renal efficiency, it was desirable to obtain, if possible, some estimate of renal efficiency in man. A number of such experiments are on record in the literature; but the results given are so discordant that it was decided to carry out the experiments again.

The experiments described below were performed on young men. These came into the hospital immediately after the evening meal, between 7 and 8 P.M., on the night before the experiment. From then until the end of the experiment at 11–12 A.M. of the next day, they remained in bed and received no food or drink, except the urea solution or water as indicated in table 1. The subjects voided during the night, the following morning on waking, and then during the experiment at the times indicated. The metabolism was determined by measuring the oxygen consumption over a period of five or six minutes by means of the McKesson "Metabolor." In order to accustom the subjects to the procedure of determining the metabolic rate, a number of determinations were made, after the subject was in bed the night before. The practice during the experiment was to obtain, at intervals of one-half hour, three consecutive values for the metabolism before administering the urea solution or water; and then for four or six half-hourly intervals afterward. Urine was collected immediately after each estimation of the metabolism. The subjects experienced no discomfort, and only brief transient sensations of any sort after the ingestion of the urea. In order to minimize the effects of water *per se*, the urea was given in very concentrated solution. Since, according to Dubois[33] it is not possible to maintain a human subject in a steady basal state for more than a few hours, the experiments as a rule began at 8:00 A.M., and all values for the metabolism taken after 12:00 noon have not been used. The urea solution was warmed to 37°C. before it was given to the subject to drink. Chlorides were determined by the Volhard-Arnold method,[4] urea, with the use of urease.

The results obtained are summarized in table 1. They show an unequivocal rise in metabolism accompanying increased excretion of urea. The calculated values given in the last column of table 1 indicate the low order of magnitude of $\Delta W/\Delta Q$. This ratio is a better measure of the working efficiency of the kidney than either of the other two efficiency ratios. The fact that the value of this ratio is of the same order of magnitude as W/Q and $W/\Delta Q$ obtained from estimations of the oxygen consumption of the isolated kidney, indicates that the sum of Q_m and Q_{iso} probably is small compared with the additional energy expended in the performance of work by the kidney. This is substantiated by the findings of Winfield, and by the oxygen consumption of the poisoned as compared with the unpoisoned kidney.

The data are not sufficiently comprehensive, however, to throw any light on the problem of the variation of the value of the ratio $\Delta W/\Delta Q$ with the quantity of work performed. It seems probable that this quotient is not a constant, but that it will vary with the amount of work performed and with the condition of the kidney, and of the animal as a whole. On the other hand, the value of two per cent for $\Delta W/\Delta Q$ seems to be a maximal rather than a minimal value.

It is obvious that the explanation for the low efficiency of renal function is to be sought in the mechanism of the production of urine. It is possible that the reabsorption of large quantities of water, according to Rehberg several hundred times the volume of the urine, with the corresponding amounts of sodium chloride and sugar, may be the process which incurs a large expenditure of energy by the kidney, and for which there is nothing to show in the urine. Nevertheless, the figures computed for the work of reabsorption of even 200 liters of water, with the corresponding amount of electrolytes and sugar, during the formation of 1000 cc. of urine, calculated as in table 1 in the previous communication, amount to only a few per cent of the energy used. It would appear that the work of such a hypothetical reabsorption is performed with a low efficiency similar to that obtained for the final formation of urine.

A low mechanical efficiency appears to be characteristic of glandular function. For example, the data quoted in Bayliss[47] give 1.5 mg. sugar, or six gram calories, as the amount of energy consumed in the secretion of one cc. of saliva, and the calculated work for the formation of saliva from blood is much less than that for urine.

These are not the first observations of an increase in metabolism following the ingestion of urea. Zuntz,[34] quoting from experiments carried out by Steck, records that in dogs there was a rise in metabolism of 0.49–0.53 calories per gm. of nitrogen ingested and in man 0.94–1.37 calories. The rise in metabolism occurred only during the first two hours, and in man only one-sixth of the ingested urea was excreted. If the values obtained by Steck in men are accordingly multiplied by six the results are the same as those recorded in table 1. Recently Lublin[35] measured the change in metabolism in men following the ingestion of large quantities of urea solution, and observed a rise in the metabolic rate in one case of 8 per cent, and in another of 12 per cent of the basal rate; the high point coinciding with the time of greatest nitrogen excretion, and not of greatest urine volume.

A rise in metabolism following the ingestion of urea has been observed also by Lusk[36] and by Grafe,[37] on whose authority, nevertheless, the conclusion has been accepted generally that the excretion of urea is not accompanied by any demonstrable increase in metabolism. This conclusion has passed unchallenged in spite of the work on the oxygen consumption

TABLE 1

THE INCREASE IN METABOLISM IN MEN DURING THE EXCRETION OF UREA

SUBJECT			TIME			EXCRETION OF CHLORIDE		EXCRETION OF UREA			
NAME	BODY SURFACE	YEARS, AGE	OF INGESTION OF UREA SOLUTION OR OF WATER	OF DETERMINATION OF METABOLISM	OF URINE PRODUCTION	VOLUME OF URINE	CONCENTRATION AS NaCl	AMOUNT PER HOUR AS NaCl	CONCENTRATION	AMOUNT PER HOUR	METABOLISM, KG. CAL. PER SQUARE METER PER HOUR	INCREASE IN METABOLISM FOR ADDITIONAL NITROGEN EXCRETION, KG. CAL./GM.
	SQUARE METERS					CC.	GM./100 CC.	GM./HR.	GM./100 CC.	GM./HR.	KG. CAL.	KG. CAL.
R. L. B.	1.77	27	at 9.38,		8.02– 8.32	25	1.08	0.54				
			37.5 cc.	8.55– 9.00	8.32– 9.02	26	1.06	0.55	0.80	0.42	36.3	
			of 40	9.25– 9.30	9.02– 9.34	30	0.98	0.55	0.78	0.44	36.4	
			per cent	9.55–10.00	9.34–10.02	35	0.82	0.83	0.96	0.97	39.8	
			Urea	10.25–10.30	10.02–10.33	64					39.0	10
			solution	10.55–11.00	10.33–11.05	41	0.94	0.69	1.19	0.87	38.0	
				11.35–11.40	11.05–11.42	43					41.3	
B. B.	1.58	26	at 9.36,	8.00– 8.05							37.5	
			37.5 cc.	8.25– 8.30	8.06– 8.31	30	1.26	0.91	0.77	0.55	36.7	
			of 40	8.55– 9.00	8.31– 9.03	27	1.24	0.63	0.65	0.33	..	
			per cent	9.25– 9.31	9.03– 9.32	28	1.24	0.72	0.60	0.35	37.3	
			Urea	9.55–10.00	9.32–10.02	31	1.08	0.74	0.81	0.55	38.6	11
			solution	10.25–10.31	10.02–10.31	36					40.0	
				10.55–11.00							40.0	
				11.05–11.12	10.31–11.05	39	0.90	0.68	1.10	0.83	39.7	
				11.25–11.30	11.05–11.32	38					41.3	
G. H. P.	1.90	19	at 7.50,		6.43– 7.49	46	1.39	0.58	0.96	0.40		
			20 gm.	7.10– 7.15							41.8	
			Urea	7.40– 7.45							42.4	
			in 35 cc.	8.10– 8.15	7.49– 8.23	39	1.18	0.81	0.73	0.50	44.0	
			water	8.45– 8.50	8.23– 8.52	40	1.00	0.83	1.08	0.90	44.0	7
				9.00– 9.05							44.1	
				9.20– 9.25	8.52– 9.32	67	0.94	0.94	1.22	1.22	43.6	

R. C. H.	1.77	21	at 8.59,	8.15– 8.22	7.53– 8.54	34.5	1.08	0.37	0.83	0.28	39.0
			37.5 cc.	8.45– 8.52							38.5
			of 40	9.15– 9.20	8.54– 9.27	22.5	1.02	0.42	0.87	0.36	39.0
			per cent	9.45– 9.55	9.27– 9.56	28.0	0.79	0.46	1.16	0.68	41.5
			Urea	10.15–10.21	9.56–10.22	25.5					40.3
			solution	10.45–10.52	10.22–10.53	28.0	0.74	0.36	1.38	0.67	38.9
				11.15–11.22	10.53–11.24	22.5					40.3
O. P. J.	1.99	21	at 9.47,	8.00– 8.06	6.30– 9.26	164	0.96	0.54	0.66	0.37	38.3
			50 cc.	8.50– 8.55							38.3
			of 40	9.45– 9.50	9.26– 9.47	20	0.96	0.55	0.66	0.38	38.3
			per cent	10.00–10.06	9.47–10.06	122	0.70	2.70	0.48	1.85	47.1
			Urea	10.30–10.36	10.06–10.38	132	0.56	1.39	0.47	1.16	45.8
			solution	11.00–11.06	10.38–11.07	85	0.68	1.20	0.76	1.34	43.4
				11.30–11.36	11.07–11.39	54	0.89	0.90	1.13	1.14	38.2
				12.00–12.15	11.39–12.45	73	1.03	0.68	1.36	0.90	39.7
				12.37–12.44							40.0
O. P. J.	1.99	21	at 8.06,	7.05– 7.12	7.18– 8.06	65	1.46	1.19	0.59	0.48	38.2
			35 cc.	7.30– 7.35							37.2
			water	7.55– 8.00							38.4
				8.25– 8.30	8.06– 8.35	59	0.93	1.14	0.40	0.49	39.2
				8.55– 9.00	8.35– 9.05	73	0.73	1.07	0.31	0.45	38.7
				9.25– 9.30	9.05– 9.35	57	0.98	1.12	0.42	0.48	38.1
R. D. M.	1.84	18	at 8.57,	8.15– 8.20							40.8
			30 cc.	8.45– 8.50	8.23– 8.54	15	1.39	0.40	0.67	0.19	40.3
			water	9.15– 9.20	8.54– 9.24	18	1.43	0.51	0.68	0.24	39.7
				9.45– 9.51	9.24– 9.53	20	1.56	0.63	0.62	0.25	38.3
				10.15–10.20	9.53–10.23	20					38.7
J.	1.66	18	at 9.02,	7.55– 8.00	7.34– 8.04	23					42.7
			35 cc.	8.20– 8.25	8.04– 8.31	16.5	1.34	0.53	1.00	0.39	44.8
			water	8.50– 8.55	8.31– 9.00	17					43.6
				9.30– 9.35	9.00– 9.39	20					43.1
				9.55–10.00	9.39–10.04	10	1.38	0.39	1.17	0.33	38.4
				10.20–10.25	10.04–10.31	13					43.2

6

11

of the isolated kidney, and in spite of the fact that the conclusions both of Lusk and of Grafe rest in each case upon only two experiments, of which the results do not agree with each other.

The experiments of Lusk were carried out on dogs. In one, 17 grams of urea dissolved in 150 cc. of water were given at 12:00 noon. At 12:45 the dog vomited. Nevertheless, a large quantity of urea must have been absorbed, because the nitrogen elimination was increased from 0.154 to 0.424 gm. per hour after the administration of the urea. The basal metabolism of this dog varied from 14.7 to 18.3 calories; the general average given is 16.2 calories. In the interval designated 1–2 (which presumably was the second hour after administration of the urea) the metabolism rose to 20.42 calories per hour, and in the third hour was 18.8 calories per hour. The results of this experiment were rejected by Lusk because the animal vomited during the first hour after administration of the urea. Benedict and Emmes[38] have shown that intestinal movements have a negligible effect on the metabolic rate; and the rise in metabolism observed here occurred over a period of two and a quarter hours after the vomiting. It is important that an increase in metabolism in this experiment was obtained both by direct and indirect calorimetry. In the second experiment a dog was given 12 gm. urea in 150 cc. water at noon, and the recorded observations on the metabolic rate were made during the third and fourth hours after the administration of the urea. No increase in metabolism was observed in this interval. On this one result is based the conclusion that the excretion of urea is not accompanied by an increase in metabolism. Our observations on human beings, and those of Zuntz, indicate that the greatest excretion of urea generally occurs in the first two hours after the ingestion of urea; after this time the excretion of urea may be little more than in the pre-administration period. It was precisely in this last period that Lusk failed to observe any increase in metabolism; the large increase observed in the first experiment, on the other hand, was in the second hour. These results are not, therefore, antithetical to those obtained by Steck, Lublin, or those given in table 1.

In Grafe's experiments, both carried out on the same human subject, 22 gm. urea were administered in 750 cc. bouillon. In one case there was a decline of 2 per cent over a period of six hours; and in the other, over a period of $3^1/_2$ hours there was a rise in metabolism of 8 per cent. Apart from the discordance of the results, these experiments of Grafe are open to the criticism, based upon the observations of Dubois, that it is not possible to maintain a human subject in a steady basal state for more than three or four hours, and results obtained after such a period cannot be considered as reliable.

The question of the energy cost of the elimination of nitrogen is obviously an important one in the elucidation of the specific dynamic action

of protein. The experiments of Lusk and of Grafe were carried out ostensibly for this purpose, and their conclusion seems justified, in spite of the discrepancies in their data, that the whole of the specific dynamic action of protein cannot be due to the work of the kidney in the elimination of nitrogen. On the other hand, their conclusion that the excretion of nitrogen by the kidney incurs no expenditure of energy is not warranted by their own data. Moreover, it is improbable from the observations on the oxygen consumption of the isolated kidney, and it is contradicted by the observations of Steck, of Lublin, and those summarized in table 1. The significance of the work of the kidney in the specific dynamic action of protein is discussed elsewhere.

The conception of the normal kidney as a chemical machine which possesses a great working capacity, but which performs its work with a very low efficiency readily lends itself to the explanation of the effects of disease of the kidney on the composition of the urine and blood.

In general there may be said to be two possible effects of disease on the kidney: one, that the diseased kidney tends to perform its normal quantity of work, but with a lower efficiency; the other, that the effect of disease is to reduce the capacity of the kidney for work. It may be expected *a priori*, since "loss of function" is one of the classical signs of disease, that the second rather than the first of the two alternative reactions to injury is the case in the kidney. The observations of Barcroft and Straub mentioned above, to the effect that caffeine, mercuric chloride, and anaemia reduce the oxygen consumption of the kidney, and at the same time change the composition of the urine so that it approximates the plasma, support this surmise. Its correctness is sustained further by the findings of Tribe, Hopkins and Barcroft,[39] and of Tribe, Harvey and Barcroft,[40] that the oxygen consumption of the kidney damaged by uranium or by diphtheria toxin was always lower, and was frequently less than half the average value obtained for the normal. The effects of cyanide and of narcotics also support this view.

The human kidney when it is diseased fails in a like manner. This is the basis of the various concentration tests for kidney function. The changes in the excretion of the inorganic constituents by the failing kidney have been emphasized less, but are more instructive here than the excretion of the organic constituents. In general the findings are that the inorganic constituents whose relative concentrations are greatest in normal urine, as compared with the blood, suffer the greatest reductions in the rates of excretion when the kidney is damaged. It is this and not the amount in the blood which appears to be the determining factor. For instance, Denis and Hobson's summary[41] of the results of their analysis of a fairly large number of cases of nephritis is: "The relative rarity of abnormally high figures for the sodium and chlorides in the blood would

therefore appear to show that these two ions are excreted by the kidney with great ease, whereas the retention of inorganic phosphates may amount to 400 per cent, and of sulfate to as much as 3000 per cent of the average normal value." They found that though the normal molar concentration of phosphates in the plasma is six times that of sulfate, in nephritis, the sulfate ion in the plasma became not only relatively, but, in some extreme cases, absolutely more concentrated than the phosphates. The normal ratios of the concentrations of the three anions, chloride, phosphate and sulfate in the urine and in the blood, is least for the chloride and greatest for the sulfate.**

It is unfortunate that the concentrations of the inorganic constituents of the urine in disease are not often given. In the experiments of Hendrix and Bodansky[42] on uranium nephritis in dogs, the data given show that the concentration of phosphates in the urine in all the animals that died fell to considerably below 0.1 per cent P_2O_5, and in the two animals that survived the concentrations, though lowered somewhat, returned to 0.1 per cent or more. Frandsen found in rabbits with uranium nephritis no such lowering of the concentration of chloride in the urine. Rather the reverse, the ability to retain chloride seemed to be impaired. This may have been due to the acidosis which is engendered in uranium poisoning, resulting in an increased excretion of chloride in compensation for the failure to excrete sulfate and phosphate and the inability to form ammonia.

To test more thoroughly this view of kidney function, it is planned to obtain more data on the concomitant variations in concentration of the constituents of the blood and the urine in health and disease.

It is possible that the efficiency of the kidney varies somewhat for each substance excreted, and further that the relationship between work performed and oxygen consumed is not linear. The available data does not seem to throw any light on this interesting problem which may be related to the problem of thresholds in renal excretion.

Summary.—1. The work of the kidney in the excretion of urine is analyzed by means of the second law of thermodynamics. It is shown that the production of either hypertonic or hypotonic urine entails work on the part of the kidney. The excretion of a urine which is the same as the plasma in all details incurs no work by the kidney.

2. The energy consumed by the kidney in man in the production of urine was found to be 6–11 kg. calories per gram of nitrogen excreted.

3. It is shown that the normal healthy kidney considered as a chemical machine possesses a great capacity for work; but performs its work with an "efficiency" probably not greater than 1–2 per cent.

4. The effect of disease is to reduce markedly the capacity of the kidney for work.

This conception of renal function is supported by the evidence in the literature of the constitution of the urine in health and disease; of the effects of drugs, metallic poisons, anaemia, cyanide and narcotics on the oxygen consumption of the kidney *in situ* and isolated, and on the constitution of the urine; and by the observations of the authors, confirming earlier observations, of the increase in metabolism in man during increased excretion of urea.

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* These definitions were suggested by Professor R. C. Tolman.

** From the observations of Davies, Haldane and Peskett[43] and of Harvard and Reay[44] it seems that the concentration of chloride in the urine in health varies between 3 times that in the plasma to only a trace. Harvard and Reay, by the ingestion of large quantities of water, reduced the concentration of phosphate in the urine to as low as $^1/_5$ that in the blood. This apparently is the lowest concentration of phosphate in the urine of healthy man on record. Even under these conditions of extreme dilution of the urine, urea and sulfate were found to be more concentrated in the urine than in the blood. Ignoring the question of threshold substances and the mechanism of renal excretion it may be stated that in the urine, chlorides normally are concentrated less and may be diluted more than phosphates. The relative concentration of sulfate is always greater than either of these.

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THE THERMAL DECOMPOSITION OF NITROGEN PENTOXIDE AT LOW PRESSURES

BY J. H. HODGES AND E. F. LINHORST

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MICHIGAN

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Introduction.—The rate of decomposition of nitrogen pentoxide at low pressures is of particular interest in connection with the theory of unimolecular reactions. Since Daniels and Johnston[1] first showed this reaction to be unimolecular, many investigations have demonstrated that the specific reaction rate is constant and reproducible, and that its unimolecular character is maintained over a wide range of conditions. The problem of the source of the energy of activation which a molecule must receive prior to its decomposition offers particular difficulties in the case of a unimolecular reaction. From the simplest point of view it would seem that this activating energy could not be received through the agency of impacts with